The combination of cited art would not have made the claimed invention obvious, or motivated one of ordinary skill in the art to have combined the cited references or to have made the claimed invention.

There is evidence of record that compositions of the art of record, including cell culture media, cell lysates and/or supernatants and other cell and protein separation media, contain impurities and potential toxins recognized by one of ordinary skill to not be pharmaceutically acceptable and/or to have an additional pharmaceutical effect which would not be considered a pharmaceutically acceptable excipient.

The Examiner is understood to rely on Breviario for a teaching of PTX3. The reference is understood to provide however, at best, a putative sequence of PTX3[1], without having produced or tested the protein. There is no teaching in Breviario of a method to make PTX3. The following statement in Breviario is apparently relied upon by the Examiner:

> "... the PTX3 gene reported here has characteristics that make it attractive as a potential marker for inflammatory conditions. PTX is clearly related to CRP and SAP, two classical diagnostic indicators of acute phase response." See, page 22196, right column, third to the last sentence of last paragraph, of Breviario.

Breviario also states however that the PTX3 protein

> "is likely to be relatively unstable." See, page 22196, left column, third full paragraph, of Breviario (emphasis added).

The applicants believe that one of ordinary skill in the art would not have believed it a straight-forward or reasonably predictable matter to have made a pharmaceutical composition, as presently claimed, from a putative protein sequence, which had not

[1] See, Figure 1 of Breviario.

been produced (according to the cited art), but which was "likely to be relatively unstable".

The Examiner admits that Breviario does not teach PTX3 in a pharmaceutical composition. See, page 2 of the Office Action of September 23, 2004.

The applicants further submit that Breviario does not suggest PTX3 in a pharmaceutical composition. The Examiner appears to be relying on Breviario to allegedly teach PTX3 in at least a solution or composition which may be a pharmaceutically acceptable solution or excipient. The Examiner appears also to be asserting that the teaching of Breviario of PTX3 as a "potential marker" may be extended, according to the Examiner, to an *in vivo* marker of "inflammatory conditions". See, page 2, last line of the Office Action of September 23, 2004.

Breviario does not suggest a pharmaceutical composition containing as an active ingredient PTX3 in a pharmaceutically acceptable excipient. The applicants have discovered a physiological effect of PTX3 which would have been unexpected even if Breviario did teach an *in vivo* use of PTX3 as a "marker for vascular involvement in disease", which it did not. Id.

The Examiner is understood to believe that the cited Rothschild patent teaches expression of "nascent proteins" in a cell free system and

> "putting said newly made proteins in pharmaceutical compositions with pharmaceutical acceptable carriers for multiple potential uses such as diagnostic kits to screen humans or other animals for the presence of certain diseases or for immunological active compositions (column 23-24 in particular). ... the ... patent allows for the translation of the newly identified protein in a pharmaceutical compositions [sic] for testing of the proteins biological properties and usefulness in a diagnostic kit or any treatment

> method." See, pages 2-3 of the September 23, 2004, Office Action.

As Rothschild does not teach or refer to PTX3 or any member of the pentaxin family referred to in Breviario, the Examiner is understood to believe that Rothschild would have made it obvious to have made any putative protein in a pharmaceutical composition for use in a diagnostic kit or any treatment method. The Examiner is requested to advise the undersigned in the event the above understanding of the Examiner's reliance on the cited references is incorrect and, in such case, further requested to clarify the record.

More than the cited Breviario and Rothschild are required to establish a *prima facie* case of obviousness.

The applicants believe that Rothschild teaches, as the title suggests, "**ELECTROPHORESIS**" of nascent proteins. Pentraxins are not discussed in Rothschild.

The nascent proteins of Rothschild are broadly described as follows:

> recombinant gene products, gene fusion products, enzymes, cytokines, hormones, immunogenic proteins, human proteins, carbohydrate and lipid binding proteins, nucleic acid binding proteins, viral proteins, bacterial proteins, parasitic proteins and fragments and combinations thereof. See, column 2, line 66 through column 3, line 8 of Rothschild.

Rothschild is understood to teach, in part, a method of cell free production of proteins which requires the use of detectable markers which are incorporated into the peptide chain of the protein as the protein is being produced. See, for example, column 7, lines 1-3; column 7, lines 16-21; and column 8, lines 47-48 of Rothschild.

The cell-free translation systems, which are apparently relied upon by the present Examiner, are described by Rothschild as being commercially available and as being well known. See, column 8 of Rothschild. Moreover, Rothschild describes that

> Examples of cell-free systems include prokaryotic lysates such as Escherichia coli lysates, and eukaryotic lysates such as wheat germ extracts, insect cell lysates, rabbit reticulocyte lysates, rabbit oocyte lysates and human cell lysates. Eukaryotic extracts or lysates may be preferred when the resulting protein is glycosylated, phosphorylated or otherwise modified because many such modifications are only possible in eukaryotic systems. Some of these extracts and lysates are available commercially (Promega; Madison, Wis.; Stratagene; La Jolla, Calif.; Amersham; Arlington Heights, Ill.; GIBCO/BRL; Grand Island, N.Y.). Membranous extracts, such as the canine pancreatic extracts containing microsomal membranes, are also available which are useful for translating secretory proteins. Mixtures of purified translation factors have also been used successfully to translate mRNA into protein as well as combinations of lysates or lysates supplemented with purified translation factors such as initiation factor-1 (IF-1), IF-2, IF-3 (.alpha. or .beta.), elongation factor T (EF-Tu), or termination factors. Id.

The cell-free translation systems of Rothschild therefore contain the same impurities that have been demonstrated by evidence in the record to not constitute a pharmaceutically acceptable excipient or solution.

Rothschild teaches that the nascent proteins containing the markers described by Rothschild produced in a cell-free system may be detected by separation using polyacrylamide gel electrophoresis (PAGE) and detection of the marker in the gel as an indication of the presence of the protein. See, column 11, lines 13-26 of Rothschild.

Rothschild's polyacrylamide gel containing the detectably marked nascent protein, along with other impurities, is not believed to suggest a pharmaceutical composition of the presently claimed invention, even if Rothschild did suggest detection

of the putative sequence of Breviario's PTX3 sequence, which the applicants believe it did not.

Rothschild suggests use of a variety of markers, however Nε-dansyllysine and coumarin are apparently preferred. See, column 12, line 58 to column 13, line 17 of Rothschild. Rothschild teaches the possibility that the addition of the marker may destroy the structure and function of the nascent protein containing the same. See, column 8, line 53 to column 9, line 11. Rothschild further teaches the unpredictability of inserting the marker in to the nascent protein in a manner which will preserve the structure and/or function of the nascent protein. Id.

In the passage referred to by the Examiner (i.e., columns 23 and 24 of Rothschild), the patent prophetically discusses the use of marker-containing nascent proteins with or without further purification in diagnostic or pharmaceutical compositions. Rothschild further prophetically discusses the use of toxic markers which are "therapeutically useful compounds" which are apparently targeted by the nascent protein to the site of action upon administration to a patient followed by release of the toxin by "electrical stimulation". See, column 23, lines 8-49 of Rothschild.

This description of Rothschild which is relied upon by the present Examiner is, at best, a wish to perform further research. There is no motivation in either Breviario or Rothschild to combine the references to make the presently claimed invention. There is no reasonable expectation from the cited art that, even if the references were combined, one of ordinary skill in the art would have expected to make the presently claimed invention without requiring further invention.

Rothschild further discusses the potential to use photocleavable markers as a means for removal of the

> "non-native portion of the marker to facilitate isolation of the protein in a completely native form." See, column 23, lines 50-54 of Rothschild.

Column 24 of Rothschild discusses the use of a photocleavable coumarin-biotin marker which is specifically detected using streptavidin coupled to magnetic beads.

Rothschild describes in Example 8 of the patent to cell-free production of "human IL-2" containing photocleavable-biotin (PCB)-coumarin attached to leucines of the protein. The example does not demonstrate that the PCB-coumarin-IL-2 produced is functionally active. The PCB-coumarin-IL-2 is isolated and reacted with streptavidin-coated magnetic beads, which are used to wash and resuspend the PCB-coumarin-IL-2 which is then illuminated to, apparently, remove the biotin and leave coumarin-IL-2.

The coumarin-IL-2 in the Example is then understood to be injected in mice and then collected from the same mice in serum and isolated from the serum with magnetic beads coated with an anti-coumarin antibody. The isolated bead-anti-coumarin antibody-coumarin-IL-2 was then apparently detected, and IL-2 quantitated with an antibody specific for rat IL-2 (even though human IL-2 was allegedly originally produced).

Example 8 of Rothschild, at best, demonstrates that a coumarin containing IL-2, of unknown functionality, is able to survive for a time in a mouse. Rothschild fails in Example 8 to teach even a pharmaceutical composition containing as an active ingredient IL-2 as, for example, there is no teaching that the IL-2 component of the coumarin-IL-2 was functional, or that the coumarin-IL was not detrimental to or rejected

by the mouse, or that the coumarin component (i.e., the marker) of the coumarin-IL was not functional or even acted contrary to the IL-2 in its actions or function in the mouse.

The applicants submit, with due respect, that the Examiner has combined the cited art with an impermissible use of hindsight. There was no motivation in the cited art to combine the references and/or to make the presently claimed invention. Even if combined, the art did not provide any reasonable expectation of successfully making the presently claimed invention without further experimentation. The Examiner's combination of cited art fails to establish a *prima facie* case of obviousness and, at best, establishes that it may have been obvious to try to make a composition containing the putative sequence of Breviario. Obvious to try however can not rise to the level of establishing a *prima facie* case of obviousness.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned in the event anything further is required.

Respectfully submitted,

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